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A Method of Synthesis of Phosphinic Acids on the Basis of Hypophosphites: VII.[1] Synthesis of Pseudo-γ-Aminobutanoyl Peptides and Other Phosphinic Analogs of γ-Aminobutyric Acid

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Abstract—A method of synthesis of pseudo-γ-aminobutanoyl peptides and other phosphinic analogs of γ-aminobutyric acid from hypophosphites is suggested. Silyl phosphonites formed by *in situ* addition of bis-(trimethylsilyl) hypophosphite to the corresponding α-substituted acrylates, styrene, or vinyl phosphonate used as unsaturated components in the synthesis react in situ with ***N*-**(ω-bromoalkyl)phthalimides by an Arbuzov reaction scheme, affording ω-(phthalimido)alkylphosphinic acids possessing β-substituted β-(alkoxy-carbonyl)ethyl, β-phenylethyl, or β-(diethoxyphosphinoyl)ethyl substituents. Acid hydrolysis of these reaction products gives the target aminophosphinic acids: phosphinic analogs of γ-aminobutyric acid.

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γ-Aminobutyric acid (GABA) is the main inhibitory neuromediator in the central nervous system [2–5]. At present three classes of actively studied GABA receptors have been identified: *a, b*, and *c*. (3-Aminopropyl)methylphosphinic acid (SK&F97541) and 3-(aminopropyl)phosphonous acid (CGP27492) are the strongest $GABA_b$ agonists [4, 5]. The main disadvantage of these compounds is their low ability to penetrate the hematoencephalic barrier. Therefore, the most prospective approach to search for effective ligands for $GABA_b$ receptors is synthesis of phosphinic GABA analogs containing lipophilic fragments, which would promote development of orally active compounds [5]. Of interest mat prove a new approach to search for effective ligands for $GABA_b$ receptors on the basis of phosphinic acid analogs of GABA-peptides: pseudo-γ-aminobutanoyl peptides **I**.

In this work we suggest a synthesis of pseudo-γ-aminobutanoyl peptides **I** and other phosphinic GABA analogs as a development of the method of synthesis of functionally substituted phosphinic acids from hypophosphites [6–11].

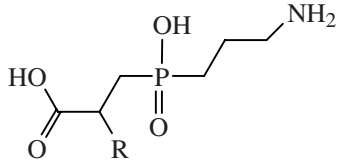
This method is based on the transformation of hydrophosphoryl compounds into silyl esters of trivalent phosphorus acids. With hypophosphites, two phosphorus–carbon bonds can be formed in a one-pot process [6–11]. Our proposed one-pot procedure makes use of hypophosphite and two equivalents of haloalkane and leads to formation of symmetrical dialkylphosphinic acids via two consecutive Arbuzov-type reactions, with silylation of a hydrophosphoryl intermediate [6–9]. The development of this methodology by using α,ω-dihaloalkanes in excess hexamethylenedisilazane [10] or the high-boiling mesitilene as a solvent [11] allowed preparation of cyclic phosphinic acids.

The one-pot procedure employing acrylates and other unsaturated compounds for forming the first phosphorus–carbon bond and haloalkanes in an Arbuzov-type reaction for forming the second phosphorus–carbon bond gave unsymmetrical dialkylphosphinic acids [12–15]. The development of this procedure by using dibromoethane and subsequent simultaneous dehydrobromination and esterification of the intermediate acid with triethyl orthofomate provided vinylphosphinates of various structure [14–

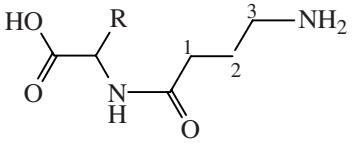
[1] For communication VI, see [1].

17]. The latter compounds were found to be useful objects for Michael addition of the amino acid function; in this way, phosphinotricin and its analogs [14], as well as γ-aminophosphinic acids (pseudo-γ-glutamyl peptides) could be synthesized [15–17].

The present work is devoted to further development of this methodology over the application of activated unsaturated compounds for forming the first phosphorus–carbon bond, followed by the application of *N*-(ω-bromoalkyl)phthalimides for forming the second phosphorus–carbon bond. Such a methodology provides a new approach to new effective ligands for $GABA_b$ receptors, specifically phosphinic pseudo-γ-butanoyl peptides **I** or GABA-pseudopeptides which are analogs of GABA-peptides **II** (peptide isosters), where one peptide bond is substituted by a hydrolytically stable methylenephosphoryl fragment.



I

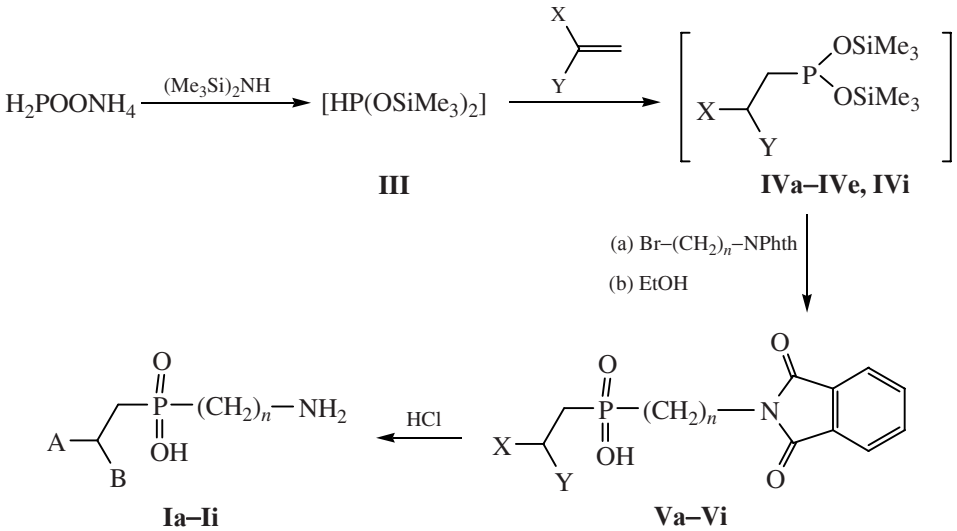


II

Such substitution is a suitable imitation of a substrate in the transition state of biological processes involving at least two different classes of hydrolytic enzymes: Zn–metalloproteinases and aspartic acid proteinases [18–20]. The use in this procedure of appropriately α-substituted acrylates allows synthesis of corresponding pseudopeptides [19–21]. For example, with ethyl acrylate as the unsaturated component, pseudo-γ-aminobutanoylglycine {γ-Abu-ψ(PO_2CH_2)Gly} (**Ia**) could be obtained; with ethyl metacrylate, pseudo-γ-aminobutanoylalanine {γ-Abu-ψ(PO_2CH_2)Ala} (**Ib**); with ethyl α-isobutylacrylate, pseudo-γ-aminobutanoylvaline {γ-Abu-ψ(PO_2CH_2)Val} (**Ic**); and with dimethyl itaconate, pseudo-γ-aminobutanoylaspartate {γ-Abu-ψ(PO_2CH_2)Asp} (**Id**) (Scheme 1).

For the unsaturated components we applied α-substituted acrylates, styrene, and diethyl vinylphosphonate. Bis(trimethylsilyl) hypophosphite (**III**) adds in situ to the C=C bond of these compounds to afford bis(trimethylsilyl) esters of [2-(ethoxycar-

Scheme 1.



III **IVa–IVe, IVi** **Ia–Ii** **Va–Vi**

A = COOH, n = 3, B = H (**Ia**), Me (**Ib**), *i*-Bu (**Ic**), $CH_2C(O)OH$ (**Id**); A = Ph, B = H, n = 2 (**Ie**), n = 3 (**If**); n = 4 (**Ih**); A = P(O)$(OH)_2$, B = H, n = 3 (**Ii**); X = C(O)OEt, n = 3, Y = H (**Va**), Me (**Vb**), *i*-Bu (**Vc**); X = C(O)OMe, n = 3, Y = $CH_2C(O)$OMe, (**Vd**); X = Ph, Y = H, n = 2 (**Ve**), n = 3 (**Vf**), n = 4 (**Vh**); X = P(O)$(OEt)_2$, Y = H, n = 3 (**Vi**).

bonyl)ethyl]phosphonous (**IVa**), [2-(ethoxycarbonyl) propyl]phosphonous acid (**IVb**), [2-(ethoxycarbonyl)-4-methylpentyl]phosphonous acid (**IVc**), [2,3-bis (methoxycarbonyl)propyl]phosphonous acid (**IVd**), [2-phenylethyl]phosphonous acid (**IVe**), and [2-(diethoxyphosphinoyl)ethyl]phosphonous (**IVi**) acids (Scheme 1).

Silyl phosphonites **IVa–IVd** enter in situ an Arbuzov-type reaction with *N*-(3-bromopropyl) phthalimide to form 2-substituted [2-(alkoxycarbonyl) ethyl][3-(phthalimido)propyl]phosphinic acids **Va–Vd** (Scheme 1) whose hydrolysis provides 2-substituted [2-(hydroxycarbonyl)ethyl][3-aminopropyl]phosphinic acids **Ia–Id**.

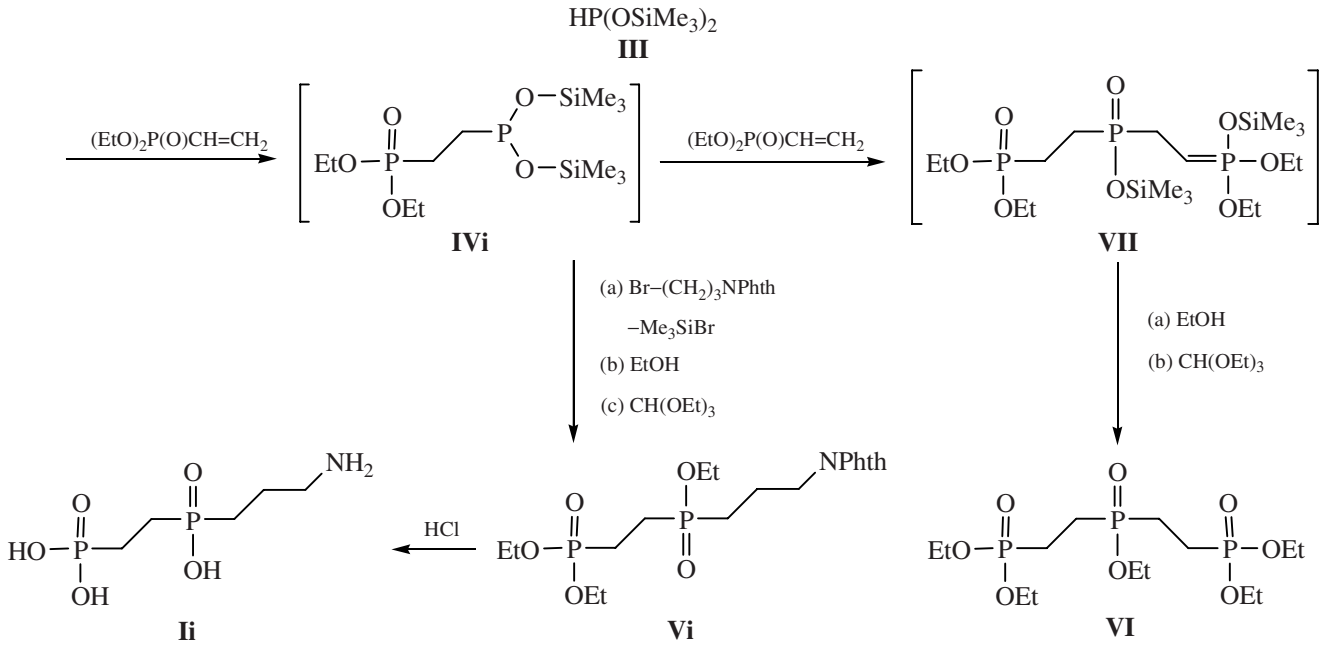
The reactions of α-substituted acrylates with bis-(trimethylsilyl) hypophosphite (**III**) were conducted under mild conditions to suppress formation of bis-adducts which, as we showed earlier [13], become the main products at a certain reagent ratio and temperature. In the case of styrene, the reaction proceeded unidirectionally [12, 14, 22] to form bis-(trimethylsilyl) (2-phenylethyl)phosphonite (**IVe**) which reacted in situ reacts with the corresponding *N*-(ω-bromoalkyl)phthalimide, affording target phosphinates **Ve–Vh**.

The reaction with diethyl vinylphosphonate provides, along with the target γ-(phthalimido) propylphosphinate (**Vi**) (Scheme 2), gave a symmetrical bis[β-(diethoxyphosphinoyl)ethyl]phosphinate (**VI**). The latter can be formed as a result of 1,2- or, more probably, 1,4-addition of the second vinyl phosphonate molecule to intermediate bis(trimethylsilyl)-[2-(diethoxyphosphinoyl)ethyl]phosphonite (**IVi**). The product of this reaction can have the structure of silyl phosphinate **VII** (Scheme 2, 1,4-addition) which can be partially dealkylated due to reaction with bromotrimethylsilane. The presence of the latter in the reaction mixture is associated with the occurrence of the target Arbuzov-type reaction of silyl ester **IVi** with *N*-(3-bromopropyl)phthalimide, leading to unsymmetrical phosphinate **Vi**. Therefore, after alcoholysis, the reaction mixture containing silyl and ethyl esters was treated with triethyl orthoformate, and both the target phosphinate **Vi** and by-product symmetrical ethyl bis[2-(diethoxyphophinoyl)ethyl]phosphinate (**VI**) were isolated as ethyl esters by chromatography on silica gel.

Hydrolysis of ω-phthalimidoalkylphosphinic acids **Va–Vi** affords ω-aminoalkylphosphinic acids **Ia–Ii** (Schemes 1 and 2) which can be considered as GABA analogs, potential ligands for $GABA_b$ receptors containing both lipophilic and hydrophilic substituents at the phosphorus atom.

Thus, we suggested a general synthesis of unsymmetrical ω-aminoalkylphosphinic acids, include-

Scheme 2.



ing pseudo-γ-aminobutanoyl peptides, starting from ammonium hypophosphite.

EXPERIMENTAL

The ^{1}H and ^{31}P NMR spectra were registered on Bruker DPX-200 and Bruker CXP-300 Fourier spectrometers against internal TMS and external 85% H_3PO_4. The melting points measured on a Boetius-PHMK device or in a block in an open capillary.

All reactions with silyl hypophosphites or intermediate phosphonous acids were performed under argon. All solvents were thoroughly dried. TLC analysis of individual compounds and reaction mixtures was carried out on Silufol (eluent chloroform–acetone, 5–7 : 1), Alufol (Kavalier), and Merck glass plates [UV-254 silica, layer thickness 0.2 mm; eluents ethanol–25% aqueous ammonia (4 : 1), isobutanol–acetic acid–water (4 : 1 : 1), or, with amino acids, pyridine–acetic acid–water–isobutanol (1 : 3 : 5 : 5)]. Amino acid were detected after spraying plates with ninhydrin, followed by drying at 110°C. Aminophos-phinic acids **I** were purified by ion-exchange chromato-graphy on Dowex 50WX8-200 (H^+) (Lancaster) and KUIKhT (H^+) (Russian Institute of Chemical Technology). Column chromatography of ω-(phthal-imido)alkylphosphinic acids **V** was carried out on Silpearl and Chemapol L100/160 silica gels. Compounds **V** was purified by column chromato-graphy on Celite filter aid (Lancaster) or a mixture of Chemapol L100/160 silica gel and Brockmann neutral alumina (80–90 : 20–10, by weight).

Ammonium hypophosphite was prepared by the procedure in [23]. Hypophosphorus acid, potassium phthalimide, hexamethyldisilazane, ethyl acrylate and methacrylate, dimethyl itaconate, and styrene are supplied by C-Reactor (Lancaster), ethyl α-isobutyl-acrylate was purchased from Khimeks (St. Petersburg). Diethyl vinylphosphonate was prepared by the earlier described procedure using triethyl orthoformate for esterification and dehydrobromination of bromoethyl-phosphonic acid [24]. *N*-(2-Bromoethyl)-, *N*-(3-bromopropyl)- and *N*-(4-bromobutyl)phthalimides were synthesized as described in [25].

Synthesis of pseudo-γ-aminobutanoyl peptides Ia–Id with α-substituted acrylates as unsaturated component. A mixture of 0.036 mol of ammonium hypophosphite and 0.072 mol of hexamethyldisilazane was stirred under reflux for 2 h [26, 27]. The reaction mixture was then cooled to 25–30°C, and 0.036 mol of freshly distilled α-substituted acrylate was slowly added dropwise. After stirring at 40°C for 2–3 h followed by adding 0.036 mol of *N*-(3-bromopropyl) phthalimide, the mixture was stirred under reflux for 6-7 h and cooled to room temperature. Alcohol, 30 ml, was then slowly added dropwise with vigorous stirring, and the mixture was refluxed for 20–30 min, after which alcohol-insoluble admixture were filtered off. The alcohol solution was evaporated, and the oily residue was partitioned between 30–40 ml of ethyl acetate and 10 ml of 0.1 N aqueous HCl. The organic layer was additionally washed with water (10 ml), dried over $MgSO_4$, and evaporated in a vacuum. The residue was dissolved in chloroform and passed through a bed of Celite (20–30 ml), evaporated, and the residue was subjected to chromatography on silica gel (eluents chloroform and chloroform–isopropanol, 20:1–2) to isolate 2-substituted [2-(alkoxycarbonyl)-ethyl][3-(phthalimindo)propyl]phosphinic acid **Va–Vd**. Commonly, acids **V** were used for preparing target amino acids **I** without further purification.

[2-(Ethoxycarbonyl)ethyl][3-(phthalimido)pro-pyl]phosphinic acid (Va) was isolated pure and characterized after additional crystallization from ether. Yield 53% (per ammonium hypophosphite), mp 94–97°C. ^{1}H NMR spectrum (CD_3OD), δ, ppm : 1.15 t (3H, CH_3), 1.72 m (2H, CH_2), 1.90 m (4H, $2CH_2$), 2.47 m [2H, $CH_2C(O)$], 3.66 t (2H, CH_2N), 4.00 q (2H, CH_2O), 7.75 m (4H, Ph). ^{1}H NMR spectrum ($CDCl_3$, δ, ppm) : 1.23 t (3H, CH_3), 1.75 m (2H, CH_2), 2.02 m (4H, $2CH_2$), 2.60 m [2H, $CH_2C(O)$], 3.77 t(2H, CH_2N), 4.10 q (2H, CH_2O), 6.85 br.s (1H, POOH), 7.70 m (2H, Ph), 7.82 m (2H, Ph). ^{31}P NMR spectrum, δ_P, ppm: 52.9 (CD_3OD), 57.9 ($CDCl_3$). Found, %: C 54.52; 54.60; H 5.61, 5.58; P 8.65, 8.51. $C_{16}H_{20}NO_6P$. Calculated, %: C 54.39; H 5.71; P 8.77.

[3-(Phthalimido)propyl]phosphinic acids **Va-Vd** were subjected to acid hydrolysis in 30–40 ml of 8 N HCl for 13–15 h. The reaction mixture was extracted with benzene, toluene, or chloroform (2 × 20 ml), the acidic aqueous phase was evaporated, and the residue was passed through a cation-exchange column (eluent 0.5–1.0 N HCl). Fractions with a positive ninhydrin reaction were collected and evaporated, and the residue was crystallized from a mixture of acetone and 0.5–1.0 N HCl. Free amino acids **I** were isolated by treatment of the residue with excess propylene oxide in aqueous alcohol.

(3-Aminopropyl)(2-carboxyethyl)phosphinic acid (Ia) [pseudo-γ-aminobutanoylglycine γ-Abu-ψ-(PO_2CH_2)Gly]**.** Yield 83% (per **Va**), mp 135–137°C (0.5 N HCl : acetone). ^{1}H NMR spectrum (D_2O), δ, ppm : 1.55 m (2H, CH_2), 1.78 m (4H, $2CH_2P$), 2.47 d t [2H, $CH_2C(O)$], 2.98 t (2H, CH_2N). ^{31}P NMR spectrum (D_2O), δ_P, ppm : 43.7. Found, %: C 31.23; 31.31; H 6.48, 6.43; P 13.11, 13.23. $C_6H_{14}NO_4P{\cdot}HCl$. Calculated, %: C 31.11; H 6.53; P 13.37.

(3-Aminopropyl)(2-carboxypropyl)phosphinic acid (Ib) [pseudo-γ-aminobutanoylalanine γ-Abu-ψ-(PO_2CH_2)Ala]**.** Yield 43% (per ammonium hypophosphite), mp 121–123°C (0.5 N HCl + acetone). ^{1}H NMR spectrum (D_2O), δ, ppm : 1.20 d (3H, CH_3; J_{HMe} 7.33 Hz), 1.80 m (5H, CH_2CH_2+ one of $CHCH_2P$ protons), 2.15 d.d.d (1H, second of $CHCH_2P$ protons), 2.75 m (1H, CHCOO), 2.95 t (2H, CH_2N). ^{31}P NMR spectrum (D_2O), δ_P, ppm : 53.3. Found, %: C 34.11; 34.17; H 7.08, 7.13; P 12.73, 12.77. $C_7H_{16}NO_4P \cdot HCl$. Calculated, %: C 34.23; H 6.98; P 12.61.

(3-Aminopropyl)(2-carboxy-4-methylpentyl)-phosphinic acid (Ic) [pseudo-γ-aminobutanoylvaline-γ-Abu-ψ(PO_2CH_2)Val]**.** Yield 47% (per ammonium hypophosphite), mp 117–119°C (1 N HCl + acetone). ^{1}H NMR spectrum (D_2O), δ, ppm : 0.60 d (3H, CH_3; J_{HMe} 7.3 Hz), 0.64 d (CH_3; J_{HMe} 7.3 Hz), 1.15 m [1H, $CH(CH_3)_2$], 1.30 m [2H, $CH_2CH(CH_3)_2$], 1.55–1.80 m (6H, $CH_2CH_2PCH_2$), 2.95 m (1H, CHCOO), 3.05 t (2H, CH_2N). ^{31}P NMR spectrum (D_2O), δ_P, ppm : 50.3. Found, %: C 39.11; 39.17; H 8.31, 8.33;P 10.03, 9.89. $C_{10}H_{22}NO_4P \cdot HCl \cdot H_2O$. Calculated, %: C 39.29; H 8.24; P 10.13.

(3-Aminopropyl)(2,3-dicarboxypropyl)phosphinic acid (Id) [pseudo-γ-aminobutanoylaspartate γ-Abu-ψ(PO_2CH_2)Asp]**.** Yield 37% (per ammonium hypophosphite), mp 215–217°C (H_2O : EtOH). ^{1}H NMR spectrum (D_2O, δ, ppm): 1.40–1.95 m (6H, $3CH_2$), 2.60 m (CH_2COO), 2.90 t (CH_2N), 2.90 m (CHCOO). ^{31}P NMR spectrum (D_2O), δ_P, ppm: 42.2. Found, %: C 35.29; 35.17; H 6.78, 6.83; P 11.33, 11.37. $C_8H_{16}NO_6P \cdot H_2O$. Calculated, %: C 35.43; H 6.69; P 11.42.

Synthesis of (ω-aminoalkyl)(2-phenylethyl)phosphinic acids Ie-Ih with styrene as unsaturated component. A mixture of 0.036 mol of ammonium hypophosphite, 0.036 mol of freshly distilled styrene, and 0.072 mol of hexamethyldisilazane [12, 14, 22] was stirred under reflux for 2 h. The reaction mixture was then cooled, and 0.030 mol of *N*-(ω-bromoalkyl)-phthalimide was added in one portion at 25–30°C under argon. After stirring for an additional 8–10 h and cooling to room temperature, 30–40 ml of alcohol was slowly added dropwise with vigorous stirring. The mixture was refluxed for 20–30 min, filtered, and evaporated in a vacuum. The residue was partitioned between 30 ml of chloroform and 10 ml of 0.1 N aqueous HCl. The organic layer was washed with water (2 × 10 ml), dried over $MgSO_4$, concentrated in a vacuum, and filtered through a bed (20–30 ml) of Celite or a mixture of silica gel and alumina (eluent chloroform). The eluate was evaporated in a vacuum and additionally passed through silica gel (eluent chloroform and chloroform–isopropanol, 20 : 1) to isolate (2-phenylethyl)(ω-phthalimidoalkyl)phosphinic acid **Ve–Vh**. Commonly, acids **V** were further used for preparing target amino acids **I** without additional purification. [2-(Phtalylimido)ethyl]- and [3-(phthalimido)propyl](2-phenylethyl)phosphinic acids **Ve** and **Vf** were isolated pure and characterized after additional crystallization.

(2-Phenylethyl)[2-(phthalimido)ethyl]phosphinic acid (Ve). Yield 43% [per *N*-(2-bromoethyl)phthalimide], mp 118–121°C (ether–alcohol). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm : 2.17 m (4H, $2CH_2P$), 2.94 m (2H, CH_2), 3.97d. t (2H, CH_2), 7.25 m (5H, Ph), 7.67 m (2H, Ph), 7.82 m (2H, Ph), 10.18 br.s (1H, POOH). ^{31}P NMR spectrum, δ_P, ppm: 55.0 ($CDCl_3$), 42.6 (D_2O + NaOD, pH 10). Found, %: C 62.81; 62.67; H 5.31, 5.51; P 8.83, 8.71. $C_{18}H_{18}NO_4P$. Calculated, %: C 62.97; H 5.28; P 9.02.

(2-Phenylethyl)[3-(phthalimido)propyl]phosphinic acid (Vf). Yield 47% [per *N*-(3-bromopropyl)-phthalimide], mp 112–113°C (ether–alcohol). ^{1}H NMR spectrum (DMSO-d_6 : CCl_4, 1:3), δ, ppm: 1.58 m (2H, CH_2), 1.83 m (4H, $2CH_2P$), 2.78 m (2H, CH_2), 3.63 t (2H, CH_2N), 7.22 m (5H, Ph), 7.80 m (4H, Ph). ^{31}P NMR spectrum, δ_P, ppm: 49.0 (DMSO + CCl_4, 1:3). Found, %: C 62.81; 62.67; H 5.31, 5.51; P 8.83, 8.71. $C_{18}H_{18}NO_4P$. Calculated, %: C 62.97; H 5.28; P 9.02.

Compounds **V** were subjected to acid hydrolysis in 40–50 ml of 8 N HCl for 13–15 h. After cooling, the reaction mixture was extracted with 15–20 ml of benzene, touene, or chloroform. The acidic aquoues phase was evaporated, and the residue was passed through a cation-exchange column (eluent 0.5–1.0 N HCl). Fractions with a positive ninhydrin reaction were collected, evaporated, and the residue was crystallized from an acetone–0.5 N HCl mixture.

(2-Aminoethyl)(2-phenylethyl)phosphinic acid (Ie), hydrochloride. Yield 83% (per **Ve**), mp 173–175°C (1 N HCl : acetone). ^{1}H NMR spectrum (D_2O), d, ppm: 1.95 m (4H, $2CH_2P$), 2.75 m (2H, CH_2), 3.07 m (2H, CH_2N), 7.21 m (5H, Ph). ^{31}P NMR spectrum (D_2O), δ_P, ppm: 54.4. Found, %: C 47.77, 47.50; H 6.39, 6.43; P 12.31, 12.17. $C_{10}H_{16}NO_2P \cdot HCl$. Calculated, %: C 48.11; H 6.86; P 12.41.

(3-Aminopropyl)(2-phenylethyl)phosphinic acid (If), hydrochloride. Yield 78%, (per **Vf**), mp 169–171°C (1N HCl : acetone). ^{1}H NMR spectrum (D_2O + DCl), d, ppm: 0.95 m (4H, $2CH_2$), 1.30 m (2H, CH_2), 1.98 m (2H, CH_2), 2.12 t (2H, CH_2N), 6.43 m (5H, Ph). ^{31}P NMR spectrum (D_2O + DCl), δ_P, ppm: 58.5. Found, %: C 49.83, 49.94; H 7.30, 7.33; P 11.69, 11.61. $C_{11}H_{18}NO_2P \cdot HCl$. Calculated, %: C 50.10; H 7.26; P 11.75.

(4-Aminobutyl)(2-phenylethyl)phosphinic acid (Ih), hydrochloride. Yield 29%, (per ammonium hypophosphite), mp 143–145°C (1N HCl–acetone). ^{1}H NMR spectrum (D_2O), d, ppm: 0.8–1.10 m (6H, $3CH_2$), 1.33 m (2H, CH_2), 2.05 m (2H, CH_2), 2.23 t (2H, CH_2N), 6.25–6.45 m (5H, Ph). ^{31}P NMR spectrum (D_2O + DCl), δ_P, ppm: 60.5. Found, %: C 51.93, 52.10; H 7.51, 7.53; P 11.09, 10.91. $C_{12}H_{20}NO_2P \cdot HCl$. Calculated, %: C 51.90; H 7.62; P 11.15.

Synthesis of ethyl [2-(diethoxyphosphinoyl)ethyl] [3-(phthalimido)propyl]phosphinate (Vi) with vinyl phosphonate as unsaturated component. A mixture of 1.5 g (0.018 mol) of ammonium hypophos-phite and 8 ml (0.036 mol) of hexamethyldisilazane was stirred under reflux for 2 h, cooled to 30–40C, and 2.8 ml (0.018 mmol) diethyl vinylphosphonate was added dropwise. The mixture was stirred at 80°C for 2 h [15], cooled to room temperature, and 4.2 g (0.018 mol) of *N*-(3-bromopropyl)phthalimide was then added in one portion under a slow argon flow. The mixture was stirred under reflux for 7 h, diluted with 20 ml of alcohol, refluxed for 1 h, and then evaporated in a vacuum. The residue was evaporated with benzene or toluene (2 × 20 ml), after which 30 ml (0.33 mol) of triethyl orthoformate was added, and the mixture was refluxed with a Dean–Stark trap to remove the ethyl acetate and alcohol formed. Excess triethyl orthoformate was removed, and the residue was chromatographed on silica gel (eluent chloroform) to isolate 2.5 g (36% per ammonium hypophosphite) of an oily compound **VI**. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.28 t (3H, CH_3), 1.32 t (6H, $2CH_3$), 1.80 m (2H, CH_2), 1.98 m (6H, $3CH_2P$), 3.74 t (2H, CH_2N), 4.07 m (6H, $3CH_2O$), 7.72 m (2H, 2CH), 7.82 m (2H, 2CH). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 31.1 d [1P, $P(OEt)_2$, J_{PP} 68.3 Hz], 55.3 d (1P, CH_2PCH_2, J_{PP} 68.3 Hz). Subsequent elution with a chloroform–isopropanol mixture (19:1) gave 0.6 g (16% per ammonium hypophosphite) of **ethyl bis[2-(diethoxyphosphinoyl)-ethyl]phosphinate (VI)** as a light yellow oil. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 1.28 t (15H, $5CH_3$), 1.92 m (8H, $4CH_2P$), 4.03 m (10H, $5CH_2O$). ^{31}P NMR spectrum ($CDCl_3$, δ_P, ppm): 30.8 d [2P, $P(OEt)_2$, J_{PP} 69.0 Hz], 54.5 t (1P, CH_2PCH_2, J_{PP} 69.0 Hz). Found, %: C 39.77, 39.61; H 8.10, 8.13; P 21.53, 21.71. $C_{14}H_{33}O_8P_3$. Calculated, %: C 39.82; H 7.88; P 22.00.

(3-Aminopropyl)[2-(dihydroxyphosphinoyl)-ethyl]phosphinic acid (Ii). A mixture of 3 g of ester **Vi** and 30 ml of 6 N HCl was refluxed for 11 h, cooled to room temperature, and phthalic acid was filtered off. The aqueous phase was extracted with benzene (3 × 15 ml), evaporated, and the residue was passed through a cation-exchanger column (eluent 0.5 N HCl). Fractions with a positive ninhydrin reaction were collected and evaporated, and the target amino acid was crystallized from aqueous acetone. Yield 1.4 g (71% per **Vi**), mp 183–188°C (foaming), 271–273°C (melting with decomposition). ^{1}H NMR spectrum (D_2O, pH 1), δ, ppm: 1.77 m (8H, CH_2), 2.92 t (CH_2N). ^{1}H NMR spectrum (D_2O, pH 9), δ, ppm: 1.27 m (2H, CH_2), 1.42 m (4H, CH_2), 1.65 m (2H, CH_2), 2.83 t (CH_2N). ^{31}P NMR spectrum (D_2O, pH 1), δ_P, ppm: 28.4 d (1P, $P(OH)_2$, J_{PP} 66.4 Hz), 54.4 d (1P, CH_2PCH_2, J_{PP} 66.4 Hz). ^{31}P NMR spectrum (D_2O, pH 9), δ_P, ppm: 22.3 d [1P, $P(OH)_2$, J_{PP} 62.7 Hz], 46.7 d (1P, CH_2PCH_2, J_{PP} 62.7 Hz). Found, %: C 20.83, 20.91; H 6.37, 6.11; N 4.83, 4.91, P 21.57, 21.53. $C_5H_{15}NO_5P_2 \cdot HCl \cdot H_2O$. Calculated, %: C 21.03, H 6.35, N 4.90, P 21.69.

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